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Case Report

Granuloma formation and occlusion of an unruptured aneurysm after wrapping

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Summary

Excessive granulomatous foreign-body reaction is a very rare complication after wrapping of intracranial aneurysms. The pathogenetic mechanisms underlying this process are unknown. We report on a patient who developed a space-occupying granulomatous abscess after wrapping of an unruptured aneurysm of the M2/M3 bifurcation. The patient underwent revision craniotomy for abscess removal. The aneurysm was explored and found to be completely thrombosed and excluded from the circulation. Exuberant granulomatous foreign-body reaction was pathologically confirmed and *Candida parapsilosis* was isolated from the pus. The patient underwent an antifungal treatment regimen and recovered with no residual neurological deficits. Our findings support the assumption that a low-grade infectious process might trigger excessive inflammatory reaction after wrapping. We suggest that this process may also result in complete thrombosis of cerebral aneurysms, which is otherwise a rarely observed phenomenon.

Keywords: Cerebral aneurysm; wrapping; cotton fibre; granuloma; thrombosis.

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Introduction

Wrapping of intracranial aneurysms is a method usually resorted to when the neurosurgeon is confronted with lesions which cannot be clipped or can be clipped only partially, due to a broad base, calcification, atherosclerotic plaques, fusiform configuration or vessels originating from the aneurysm body [10]. Various types of materials are used for reinforcement of the aneurysm wall by wrapping, including cotton, muslin (cotton gauze), gelatine sponge, cellulose, histoacryl, muscle, fascia, and fibrin glue [8, 25]. Due to the successful stabilisation of the aneurysm wall in most cases, this method is an accepted alternative for the treatment of lesions that are not amenable to clipping [9].

Cotton wrapping of aneurysms induces a local granulomatous foreign-body reaction, resulting in thickening and fibrosis of the adventitia and thereby stabilisation of the vascular wall [28, 29]. A rarely reported, but detrimental complication of cotton wrapping is an excessive inflammatory reaction, leading to formation of space-occupying granulomatous tissue [7, 15, 19] or to a specific meningeal inflammation process known as optochiasmatic arachnoiditis [11, 24, 27]. It is not known why these complications occur in a small subgroup of patients, while the majority are not affected [3].

We describe a patient who developed a space-occupying lesion after wrapping of an incidental middle cere-

bral artery (MCA) aneurysm. *Candida parapsilosis* was isolated from the tissue after the patient underwent a re-exploration. Extensive foreign-body granuloma formation was confirmed on histopathology examination. Interestingly, the aneurysm was found to be thrombosed and fully excluded from the circulation.

Case report

We report on a 67-year-old female who underwent evaluation for non-specific vertigo. As an incidental finding, the cerebral MRI demonstrated a left sylvian lesion, suspicious of an unruptured MCA aneurysm. Digital subtraction angiography confirmed a broad-based, poly-lobulated aneurysm of the M2/M3-bifurcation with a maximal diameter of 10 mm (Fig. 1A). The decision for surgical treatment of the asymptomatic lesion was made due to an estimated annual bleeding risk of 1–2% and a life expectancy of about 20 years [18, 31], After a typical fronto-temporal craniotomy and exploration of the aneurysm, clipping was considered impossible due to prominent atherosclerotic plaques in the aneurysm walls. Application of the aneurysm clip led to occlusion of two M3 branches of the aneurysm body. The decision for wrapping with cotton gauze and fibrin glue was made intraoperatively. The patient had an uneventful postoperative course without neurological deficits. A computer tomography scan prior to discharge demonstrated normal postoperative findings.

Eighteen months later, the patient was readmitted with acute onset of headaches and vomiting as well as progressive left-sided hemiparesis and gait disturbance. Cerebral MRI demonstrated a left-sided space-occupying mass lesion measuring $43 \times 32 \times 36$ mm with cystic components and extension into the sylvian fissure (Fig. 2). There was prominent perifocal brain oedema with compression of the left ventricle, subfalcine herniation and onset of occlusive hydrocephalus. Digital subtraction angiography demonstrated indirect signs of mass effect with dislocation of the MCA and anterior cerebral (ACA) branches and non-specific diffuse vascular blush. Interestingly, perfusion of the aneurysm was not detectable, and two M3 branches were found to be occluded (Fig. 1B). The patient was afebrile, and there were no systemic signs of infection (WBC $7.3 \times 10^3/\mu l$, CRP 10 mg/l). After initiation of an empirical antibiotic treatment regimen consisting of ceftriaxone, ornidazole and vancomycin based on suspicion of brain abscess, the patient underwent a re-exploration for removal of the lesion. Intraoperatively, a partially encapsulated, purulent mass that involved the brain and subarachnoid space of the sylvian fissure was found and removed (Fig. 3A). The aneurysm was explored and found to be completely thrombosed and excluded from the circulation (Fig. 3B). Histopathological examination revealed granulomatous

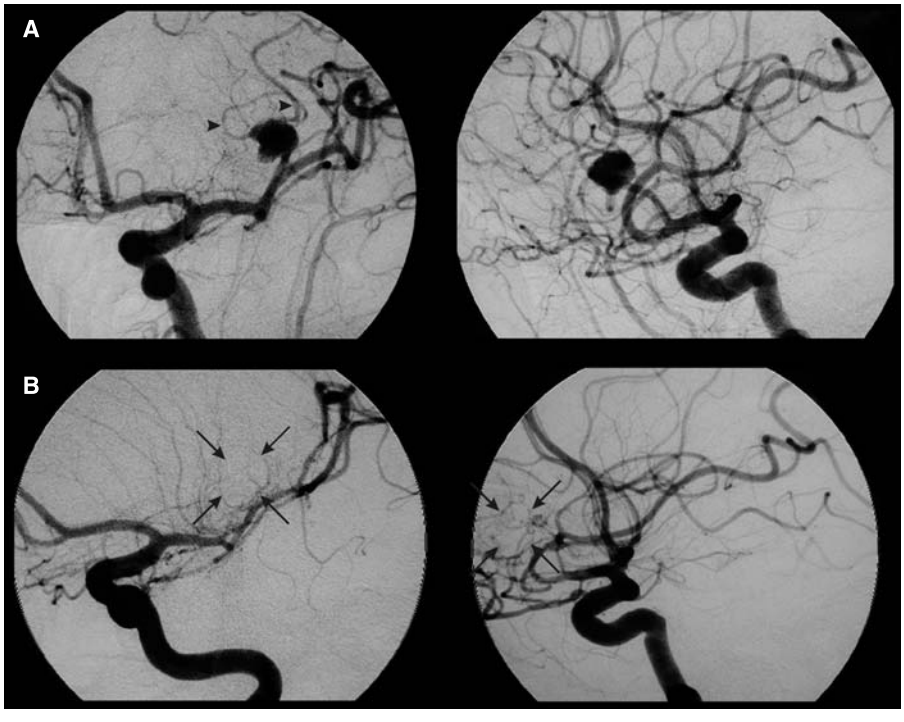

Fig. 1. Preoperative transfemoral digital subtraction angiogram demonstrating a broad-based, poly-lobulated aneurysm of the M2–M3 bifurcation with two vessels (*arrowheads*) originating from the aneurysm body (A). 18 months later, angiography demonstrates (B) complete occlusion of the aneurysm including the neck (*arrows*). In addition, the two M3 branches originating from the aneurysm body were found to be occluded

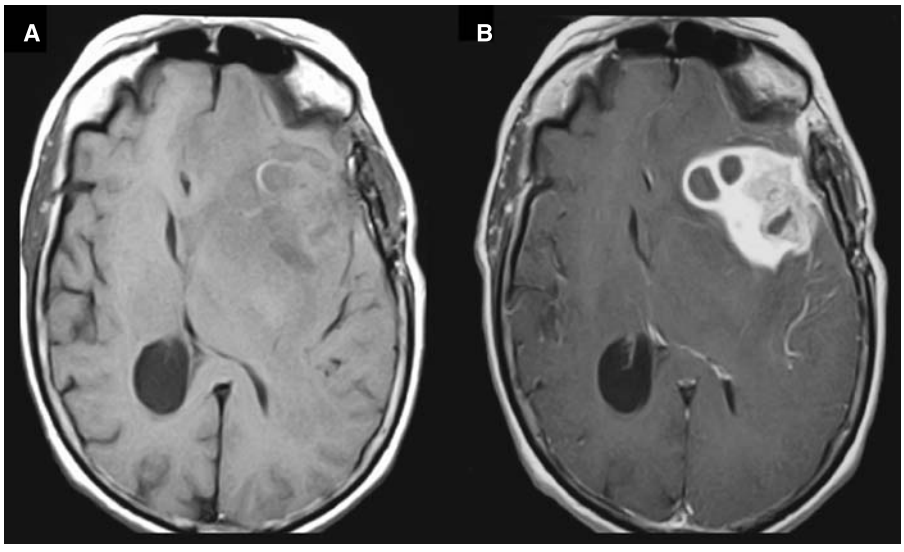

Fig. 2. Native (A) and gadolinium-enhanced (B) T1-weighted MR tomography demonstrating a non-homogeneous contrast enhancing mass in the anterior part of the left sylvian fissure with low signal on native T1-weighted images. There is significant mass effect with midline shift, subfalcine herniation and unilateral obstructive hydrocephalus

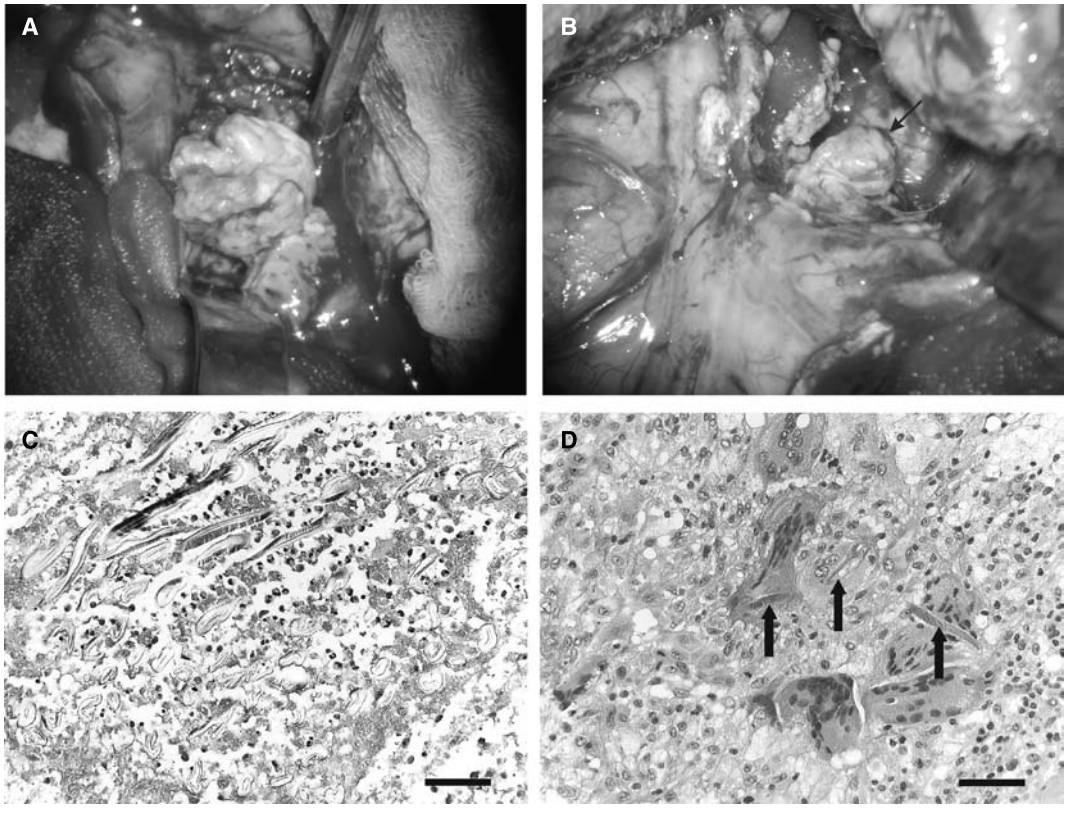

Fig. 3. Intraoperative images demonstrating the space-occupying granulomatous tissue in the left sylvian fissure (A). After removal of the mass lesion and microsurgical exploration, the fully thrombosed aneurysm is clearly visible (B, *arrow*). The histopathological examination (Paraffin section, H&E stain) revealed cotton fibres embedded in the purulent mass with granulocytes in various stages of decay in granulomatous tissue (C). Fibre fragments (*arrows*) were detected within multinucleated giant cells of the foreign body type in H & E stained paraffin sections (D). Scale bars = 120 μm

tissue with encapsulated cotton fibres and reactive gliosis of the adjacent brain tissue. There was marked presence of foam-cell reaction, granuloma formation with giant cells of foreign-body type, birefringent foreign body material, which was partially phagocytosed in giant cells, and perivascular and interstitial lymphogranulocytar infiltrate (Fig. 3C, D). Periodic acid-Schiff (PAS) and silver methamin staining for fungal elements were

negative. However, *Candida parapsilosis* was isolated from the microbiological cultures. The antibiotic treatment was therefore discontinued. Under an antifungal treatment regimen with liposomal amphotericine-B ($1 \times 300\,mg/d$ for 6 weeks) and ketoconazole ($4 \times 200\,mg/d$), the patient recovered with no residual neurological deficits. Follow-up MR including time of flight angiography after 12 and 24 months revealed discrete amounts of persisting, contrast-media enhancing granulation tissue along the insular MCA branches. Treatment with ketoconazole was continued until complete radiological disappearance of the signs of infection was achieved.

Discussion

In situations when an intracranial aneurysm is not amenable to surgical clipping or endovascular treatment, reinforcement of the aneurysm wall by wrapping or coating the aneurysm is an accepted alternative in order to achieve a decreased risk of bleeding [8, 10, 25]. Due to improvements in both microsurgical and endovascular treatment strategies, this situation has become increasingly rare [16, 22]. A variety of materials have been proposed and used for this purpose, with varying success [8, 25, 29]. Cotton and muslin are the materials of choice by most authors and have been used since the late 1950 s [26]. In animal models, cotton was proposed to be the most suitable material for wrapping an aneurysm because it has been found to induce a perivascular fibrotic scar, thereby strengthening the blood vessel wall [28, 29]. However, the local fibrotic reaction induced by cotton fibres has been reported to extend beyond its intended location in some cases. This exuberant inflammatory response can result in severe complications, including local mass effect, headaches, seizures, visual disturbances and hypothalamic-pituitary axis dysfunction [6, 7, 19]. In addition, systemic signs of immune response like lethargy, fever and chills have been reported.

This inflammatory process has been reported to become clinically manifest either as localised formation of granulomatous tissue (so-called 'gauzoma' or 'muslinoma') or as diffuse muslin-induced arachnoiditis, which is usually optochiasmatic [4]. These entities were first reported in 1978 [23] and only about 25 further reports can be found in the medical literature. About 90% of these involved women and presented with aneurysms in particular of the anterior circulation. In such instances of adhesive arachnoiditis, optic neuropathy tends to develop secondary to the inflammatory process causing visual loss beginning 1–24 months after surgery. According to the literature, longer delays up to 54 months post-surgery may also occur [3]. The underlying mechanism responsible for the rare event of exuberant inflammatory reaction after aneurysmal wrapping is not known. In one of the few examples reported so far, bacterial infection with *Staphylococcus epidermidis* has been identified [19]. Interestingly, some of the patients with granuloma formation had pyrexia and some who underwent cerebrospinal fluid (CSF) examination demonstrated CSF pleocytosis [6, 7].

Multinucleated foreign body giant cells form by blood-borne monocyte-derived macrophage fusion [2]. Recent studies directed towards developing a better understanding of the molecular and cellular basis of this process revealed that at least one cytokine, the CC chemokine ligand 2/monocyte chemo-attractant protein 1(CCL-2/MCP-1), which is released by monocytes following phagocytosis and acts as a chemotactic mediator, participates in macrophage fusion and foreign body giant cell formation [21]. Since up-regulation of CCL-2/MCP-1 expression is a critical step in immunological defence against certain pathogens, such as bacteria, viruses and fungi [1, 17], it appears reasonable to assume that a co-existing infectious process could play a precipitating role for initiating or maintaining excessive foreign body granuloma formation after wrapping, as previously suggested by Kirollos *et al.* [19]. This assumption is further supported by the good response to antimycotic treatment in our patient.

Complete spontaneous thrombosis of intracranial aneurysms is an unusual event. Even in giant aneurysms, which are frequently characterised by partial luminal thrombosis [30], a complete spontaneous thrombotic occlusion of the aneurysmal lumen is rare [12]. After cotton wrapping of an aneurysm of the MCA trifurcation, a single example of thrombosis of the aneurysm and the whole MCA has been reported [13]. In this patient, the formation of a granuloma was also observed. Another group reported a patient with disappearance of a basilar tip aneurysm three years after wrapping [5]. Therefore, it might be possible that either the muslin-induced inflammatory reaction or a circulatory disturbance due to local swelling in the case of a space-occupying granuloma resulted in aneurysmal thrombosis. Moreover, *Candida* species are known to possess thrombogenic properties and avidly adhere to the subendothelial extracellular matrix [20]. Thus, *Candida* has a propensity to induce thrombogenic vasculitis. Involvement of major cerebral vessels, however, is rare and has been reported in only

few cases [14]. Thromboses due to fungal infections that were restricted to focal lesions, such as intracranial aneurysms, have never been reported previously. In our patient, it remains open if the granulomatous reaction or the fungal infection was responsible for the complete aneurysmal thrombosis.

In conclusion, extensive foreign body granuloma formation with space-occupying effects is an uncommon condition after aneurysmal wrapping and occurs with a very low incidence. This process may also result in complete thrombosis of cerebral aneurysms, which is otherwise rarely observed. Low-grade infections have been suspected to trigger this exuberant inflammation response in a previous report [19]. Our findings with confirmed growth of *Candida* species in the microbiological samples from the granulomatous tissue support this contention. Intracranial cotton or muslin application has to be treated like other implantation of foreign material, e.g. ventriculo-peritoneal shunts, and strict practice of the aseptic technique is mandatory. The usage of cotton wrapping for the treatment of intracranial aneurysms should be limited to the situations where no other treatment strategies are available.

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Comment

The authors describe an interesting case report that deals deeply with the pathophysiology of aneurysmal wrapping.

Wrapping or coating of ruptured cerebral aneurysms was an acceptable method of surgical treatment until the end of 1980s, as Todd *et al.* convincingly demonstrated that wrapping does offer some protection from re-bleeding in the first 6 months, but the late re-bleeding rate following wrapping is unacceptably higher than the natural history itself [1]. Since that time, most surgeons continue to deploy external wrapping as an adjuvant therapeutic option only if complete obliteration by direct clipping cannot be accomplished.

Wrapping itself is not without its own undesirable consequences. Wraps of autologous tissues become necrotic, and then are absorbed within 2 months. Although muslin is considered most effective, and therefore was also used in the present case, at times it evokes undesirable side effects such as visual failure, cranial nerve palsies or infection [2]. These side effects are based on progressive optochiasmal arachnoiditis, granulomatous reaction ('muslinoma') or ischaemia [2]. Synthetic coatings are also reported to evoke unacceptable complications such as histotoxicity, arterial occlusion and arterial wall necrosis with re-bleeding [2].

The reported clinical history of the patient who developed focal progressive neurological deterioration following spontaneous thrombosis can be also attributed to the acute swelling of the aneurysmal mass. This pattern of consecutive clinical changing represents a previously described clinical course of unruptured aneurysm [3]. In this context, intracranial aneurysm must be regarded as dynamic lesions with respect to growth and intraluminal thrombus formation [2, 3]. Based on pathophysiological explanations [3, 4], this patterns may be independend on any inflammatory reaction as described in the present case by the authors and is therefore accidentally associated with the wrapping.

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